Improving Linkages in the Source-to-Outcome Continuum

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Building a scientific foundation for sound environmental decisions

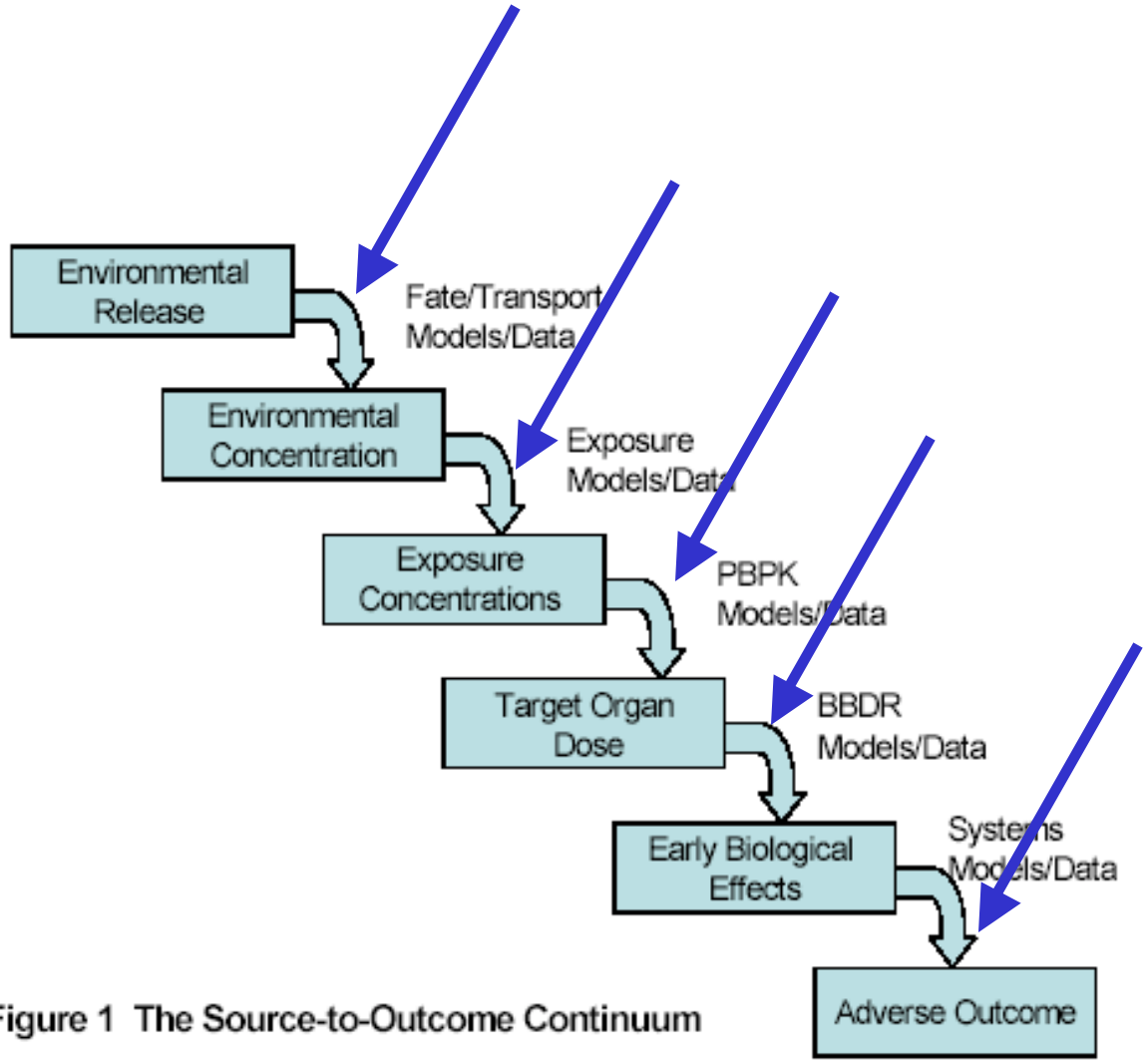

Figure 1 The Source-to-Outcome Continuum

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Research Focus Areas

- Chemical transformation
- Metabonomics
- Molecular indicators
- Dose metrics
- Toxicity pathways
- Systems biology
- Computational infrastructure

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} Predictive Toxicity

} Enhanced QRA

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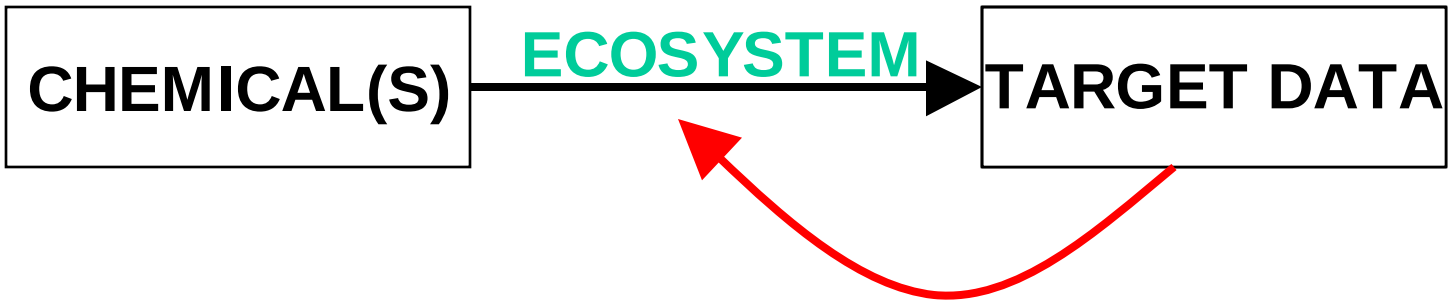
Chemical transformation

- **Chemical Fate Models**
  - Determine biologically relevant chemical in mixtures
  - Determine minimal concentrations at which biological events occur
  - Focus studies on crucial biotransformation



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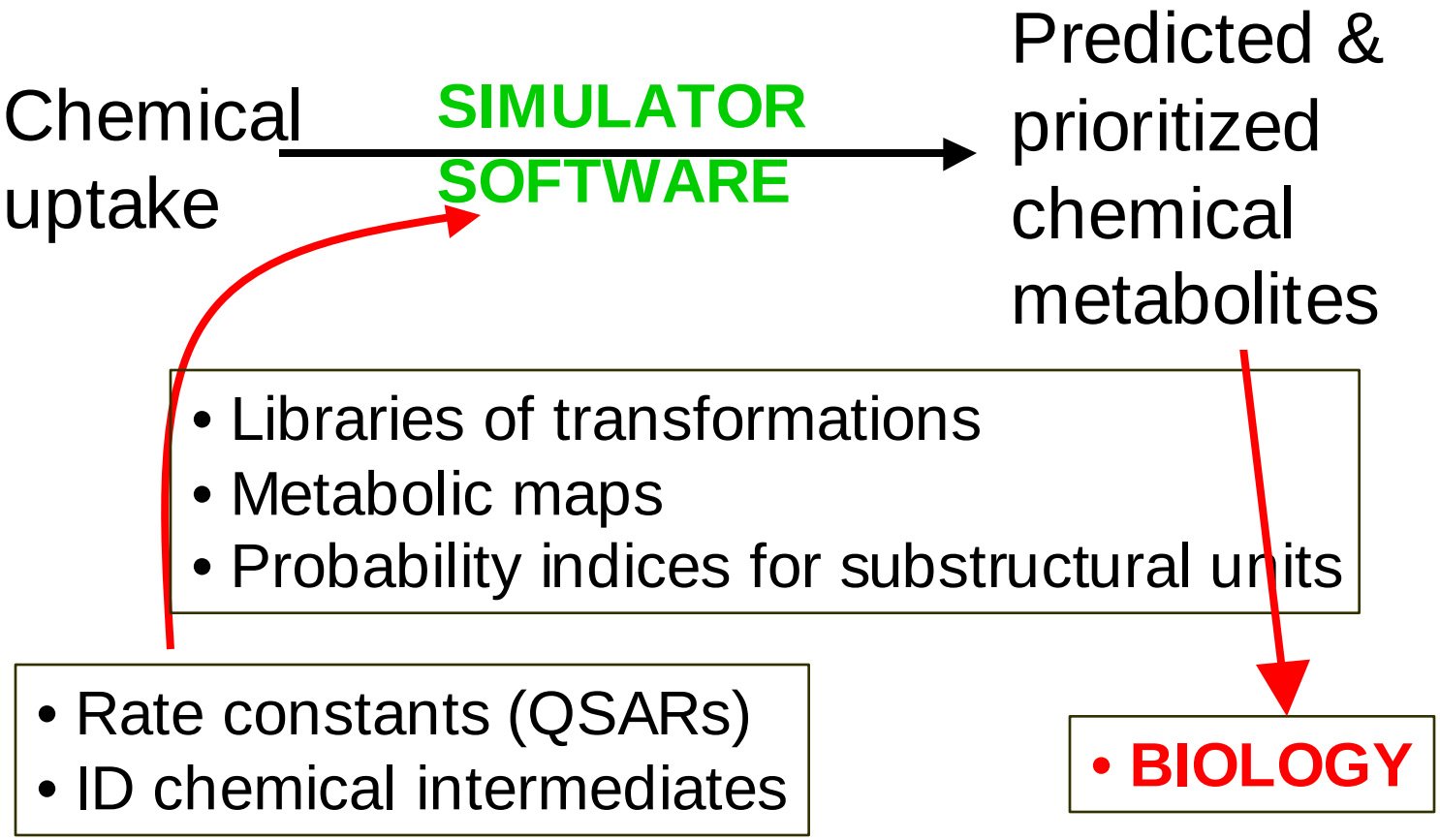
Metabolic Simulation



Nuclear magnetic resonance

- ORD / Athens, GA / 600 MHz wide-bore NMR in 2004

- NMR brings real-time measurement of chemicals / biochemicals to tissue / whole organisms samples

Metabonomics

- C&E News – “New ‘Ome in Town”
- Elucidate changes in metabolic patterns for range of endogenous metabolites
  - **Intermediary metabolites (any tissue)**
- Generate NMR spectral profiles for chemicals
- Build models to evaluate effect of novel chemicals on endogenous metabolites

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Molecular Diagnostics

- Few environmental stressors have specific or sensitive indicators
- Exposure indicators are poorly correlated with effects
- Molecular indicators could validate fate and transformation models
- Essential for integrated approach to risk assessment
- Crucial for mixtures risk assessment

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EHP, December 2002

- Feron et al. state that “the use of gene expression technologies such as microarrays is most suitable to detect joint or interactive effects of chemical mixtures.”

- Suk et al. state that “…begin to define those characteristics that are sufficiently similar to allow extrapolation of data from one mixture to another.”

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Genomics / JGI partnership

- JGI
  - Fathead minnow (*Pimephales promelas*)
    - High throughput sequencing of DNA libraries
  - Frog (*Xenopus tropicalis*)
    - Complete sequence; cDNA libraries
- EPA/ORD
  - Characterize gene regulation and androgen dose and elucidate toxicity pathway
  - Develop short term assays

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Dose Metrics

- Dose is often inferred from stressor uptake
- Dose models stand to be enhanced with specific data on stressor interactions with molecules initiating toxicity pathways
- Genetic polymorphism data will reduce uncertainty stemming from assumptions of homogeneous populations
- Susceptibility indicators will be developed for input into exposure models

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Nature, March 2003

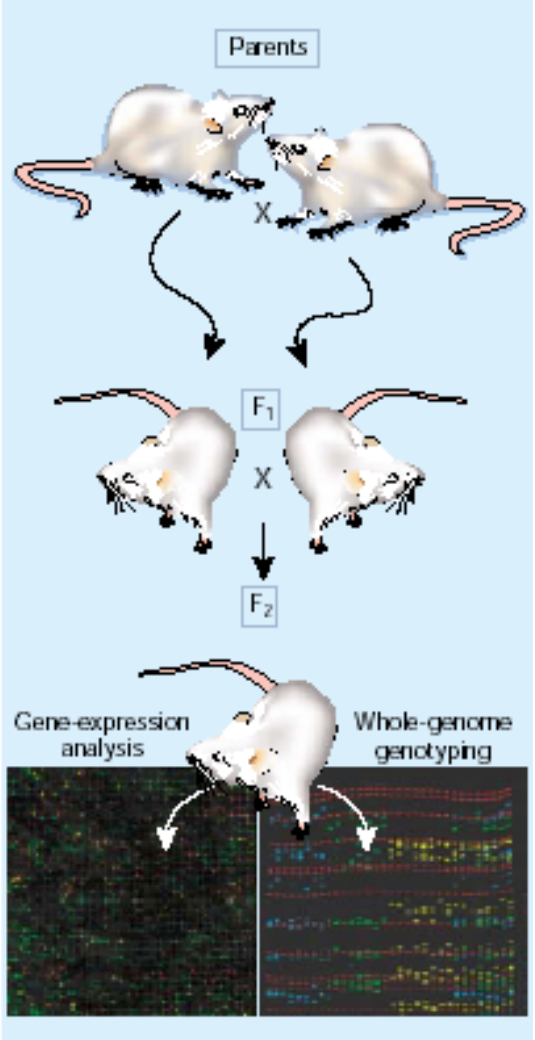
Genomics

Gene expression meets genetics

Ariel Darvasi

Genetic analyses look for differences in gene sequence that could explain variation in physical traits. Gene-expression studies provide a snapshot of active genes. These approaches are now combined, to great effect.

There is an undeclared dispute among researchers who study complex traits — The idea of carrying out genome-wide genetic analyses of gene-expression data was



Whole-genome genotyping can be related to gene expression profiling to identify genes underlying complex phenotypes (e.g., disease)

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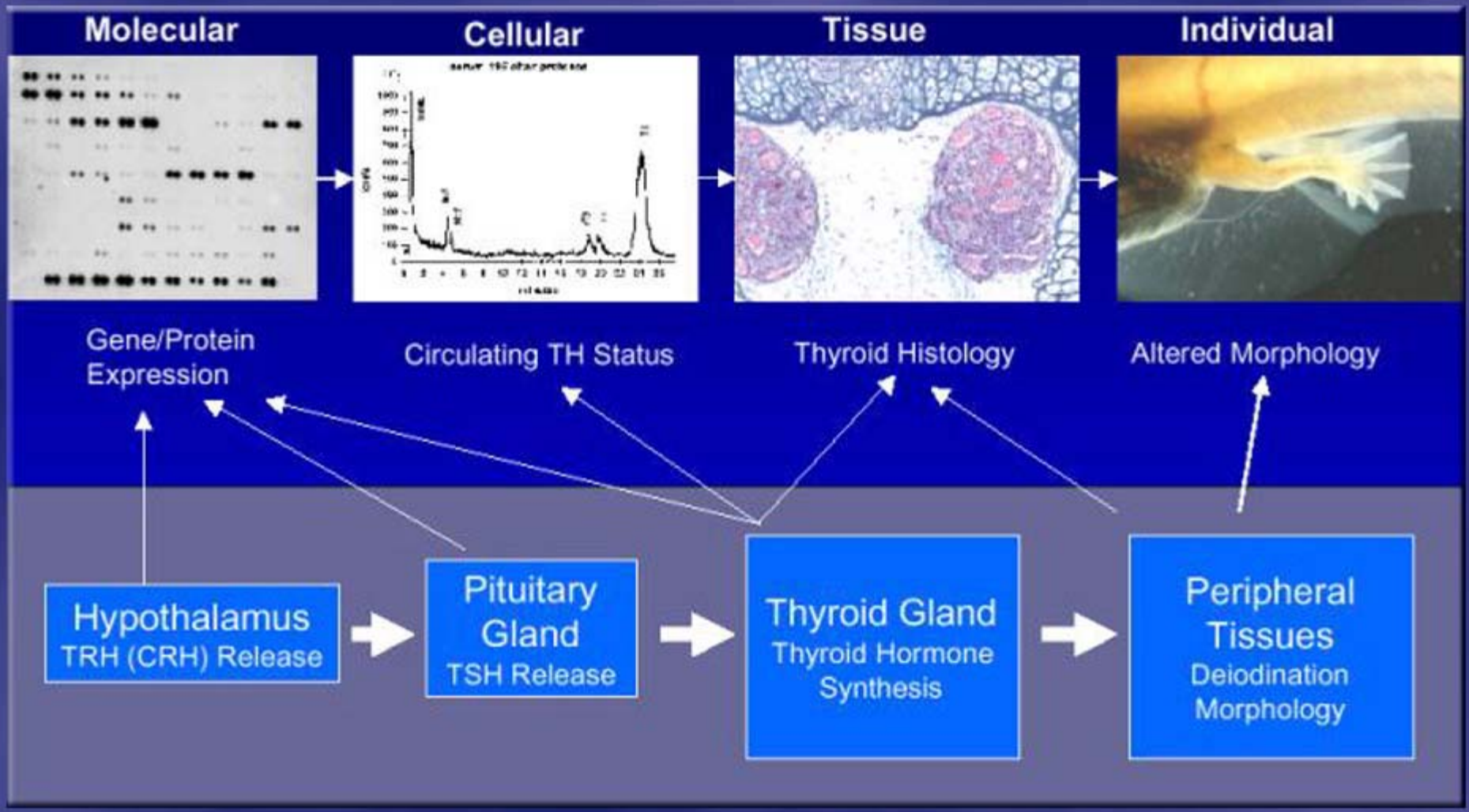
Understanding Toxicity Pathways

- Identification of discrete molecular initiating events
- Linking adverse outcomes to molecular alterations
- Elucidating linkages across biological levels of organization
- Biological basis for cross-species extrapolation
- Prediction of possible interactions for untested chemicals and mixtures

Xenopus Metamorphosis Model for Thyroid System Disruption



Systems Biology

- Computational models that reconstruct a cell, organ or organism's function from component parts

- Allows validation and simulator experiments that build confidence in predictive ability of adverse effects

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Modeling Frameworks and Uncertainty Analysis

- Standardize format and interchange protocols for information generated by computer simulation
- Technology for linking required databases
- Perform uncertainty analysis methods analysis

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- Low dose-response assessment
- Mixtures / components assessment
- Cross-species extrapolation
- Integrated assessment of both exposure / effects

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